Mechanisms and consequences of phase variation in bacterial immune systems

Supervisory team:
Main supervisor: Prof Mark Szczelkun (University of Bristol)
Second supervisor: Dr Thomas Gorochowski (University of Bristol)
Prof Nigel Savery (University of Bristol)

Host institution: University of Bristol

Project description:

Bacteria are subject to many types of cellular stress. One example is infection by viruses called bacteriophages (or simply, "phages"). To prevent infection, many different types of immune systems have evolved, including the restriction-modification (RM) and CRISPR-Cas enzymes that have been exploited for genetic engineering and genome editing, respectively. While CRISPR-Cas is an example of an "adaptive" system that can change specificity as phages evolve, the RM enzymes are considered an unchanging "innate" system. However, there are certain Type I RM systems called "shufflons" that can more rapidly adapt through genetic inversions of the gene (recombination) that encodes the protein that recognises the phage sequences and targets them for cleavage. This is a form of phase variation. One hypothesis is that spontaneous recombination events within cells produces sub-population of bacteria that encode different RM system, thus making it more difficult for phages to overcome the defences. An alternative hypothesis is that the benefit of the shufflons is that recombination brings about a change in epigenetic DNA methylation patterns that in turn change global gene expression, so that sub-populations of bacteria have different phenotypes, for example allowing cells to overcome human immune defences. All this genetic plasticity brings a potential cost, since the shuffling events may result in the autoimmune cleavage of the host genome by the endonuclease.

In this collaborative project between the Szczelkun and Gorochowski labs, you will study the Type I RM shufflons by combining biochemical analysis of purified proteins, cell-based reporter assays, nanopore sequencing, and mathematical modelling to simulate shuffling and its consequences. A first key aim is to explore whether the enzymes have evolved to favour frequent or rare shuffling and accordingly, why the shuffling process is not toxic to cells. A second key aim is to understand how the Type I RM enzymes can accommodate rearrangements in protein structures while retaining activity. The third key aim is to explore whether the shufflons can be exploited as the basis for a rationally designed synthetic genetic switch system.

You will be based in the Szczelkun lab which is supported by funding from the BBSRC and ERC, and is part of the thriving and collegiate School of Biochemistry at the University of Bristol. There will be close collaboration with the Gorochowski lab in the School of Biological Sciences providing access to synthetic biology tools and techniques. For more information on the team, see www.bristol.ac.uk/biochemistry/people/markd-szczelkun/overview.html.